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REVIEW PAPER

# A novel and alternative approach to controlled release drug delivery system based on solid dispersion technique

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Release mechanism;
Solid dispersion

**Abstract** The solid dispersion method was originally used to improve the dissolution properties and the bioavailability of poorly water soluble drugs by dispersing them into water soluble carriers. In addition to the above, dissolution retardation through solid dispersion technique using water insoluble and water swellable polymer for the development of controlled release dosage forms has become a field of interest in recent years. Development of controlled release solid dispersion has a great advantage for bypassing the risk of a burst release of drug; since the structure of the solid dispersion is monolithic where drug molecules homogeneously disperse. Despite the remarkable potential and extensive research being conducted on controlled release solid dispersion system, commercialization and large scale production are limited. The author expects that recent technological advances may overcome the existing limitations and facilitate the commercial utilization of the techniques for manufacture of controlled release solid dispersions. This article begins with an overview of the different carriers being used for the preparation of controlled release solid dispersion and also different techniques being used for the purpose. Kinetics of drug release from these controlled release solid dispersions and the relevant mathematical modeling have also been reviewed in this manuscript.



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**Contents**



## 1. Introduction

Many problems are associated with conventional multiple dosing regimen of long acting therapy, such as systemic accumulation of the drug leading to side effects or toxicities, irregular profile of the plasma drug level, and poor patient compliance. Controlled release drug delivery systems have the potential of solving these problems. Controlled release systems are the methods that can achieve therapeutically effective concentration of drug in the systemic circulation over an extended period of time with better patient compliance. Various approaches ranging from coated tablets and gels to biodegradable microparticles and osmotic systems have been used in an attempt to sustain the drug release from dosage forms. In most of the controlled release formulations, immediately upon placement in the release medium, an initial large bolus of drug is released before the release rate reaches a stable profile. This phenomenon is typically referred to as 'burst release'. Burst release leads to higher initial drug delivery and also reduces the effective life time of the device. For controlling drug release, the solid dispersion method is an alternative approach. Solid dispersion methods have been used widely in various formulations to increase dissolution rate and bioavailability of poorly water-soluble drugs.[1–7] Solid dispersion in general releases the drug immediately to maximize the absorption. Preparation of matrices with water insoluble and water swellable polymers using solid dispersion technique is a valuable method in the production of controlled release products. Many studies have been reported in the literature for the preparation of controlled release system using solid dispersion technique.[8–14] The controlled release solid dispersions are generally prepared by any of the methods: by dissolving the ingredients in a solvent followed by drying, or by melting the active and inert ingredients together followed by solidification, or a combination of the two methods. In solid dispersion, the dissolution of active ingredient is affected by the presence of other components, in particular the carriers. These carriers include ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose acetate phthalate, ethyl acetate, chitosan, and methacrylic acid copolymers. The structure of the solid dispersion is monolithic wherein the drug molecules homogeneously disperse and it has a great advantage of avoiding the risk of burst release concerning the reservoir type controlled release preparations. Despite an active research interest, there is no commercial application of controlled release solid dispersion in dosage form design. Improvement of solubility and bioavailability of poorly water soluble drugs using solid dispersion technique has been reviewed by many authors.[15–22] However, until now there are no reports in the literature on review of controlled drug delivery system using solid dispersion technique. This article provides an overview of current research on controlled release drug delivery system using solid dispersion technique.

## 2. Carriers used in controlled release solid dispersions

Water insoluble carriers are generally used to produce controlled release solid dispersion. The properties of the carriers have the major influence on the release profile of the dispersed drug. Fig. 1 shows the chemical structure of some carriers used for the preparation of controlled release solid dispersion.

### *2.1. Ethyl cellulose [EC]*

Ethyl cellulose, an ethyl ether of cellulose, is a long chain polymer of β-anhydroglucose units joined together by acetal linkages. It is a hydrophobic polymer and is used extensively as a coating material for the preparation of microcapsules, microspheres and tablets, a binder for the preparation of conventional as well as matrix type controlled release tablets, etc. It is also used in solid dispersion for water soluble drugs, or sparingly water soluble drugs. Various concentrations of EC have been used for the preparation of dimenhydrinate controlled

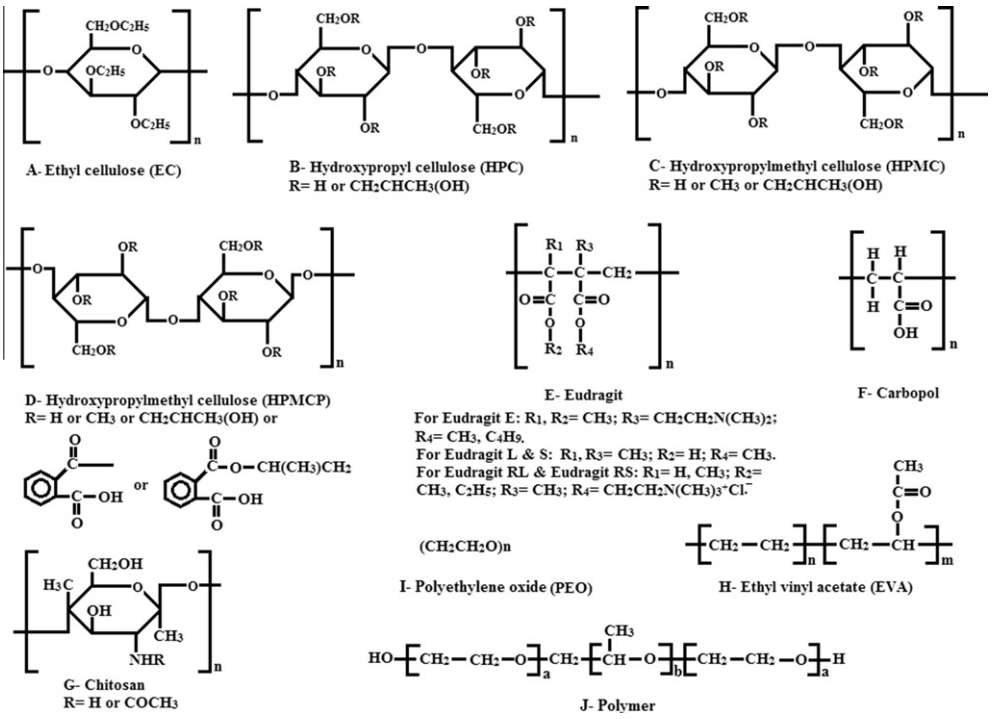


**Figure 1** Structural formulae of some controlled release solid dispersion forming carriers.

release solid dispersion using solvent evaporation technique.[23] Differential scanning colorimetry [DSC] and X-ray diffraction [X-RD] studies indicated that the drug is dispersed amorphously in the EC matrix. Infrared spectroscopy [IR] study revealed that there was no chemical interaction of the drug with EC, even in the amorphous state when the granules were prepared by the solid dispersion method. There was no significant change in the crystalline properties of the drug in the granules after exposure to 40% and 68% RH. However, on exposure to 100% RH, the granules with 1:1 drug: EC content showed the formation of hydrates of the drug. It has been observed that the amount of EC used for solid dispersion has a direct effect on the release rate of the drug. For example, the drug release reduced to about 26% with 1:5 drug-polymer ratio. Iqbal et al.[24] developed a controlled release tablet dosage form of naproxen by employing the conventional wet-granulation method and the solid dispersion method using EC as the rate controlling polymer. Tablet prepared by wet granulation method containing 6% EC released 84% of the drug in 12 h, while the formulation containing 28% EC the release rate dropped to 30% in 12 h. Similarly, tablets prepared by solid dispersion technique with 4% EC showed 88% of the drug released in 12 h, while the formulation containing 45% EC the release rate dropped to 30% in 12 h. The in vitro release study indicated that solid dispersion requires lower amounts of the polymer [~4%] than wet granulation [~6%] to produce similar release profiles. Table 1 presents some of the drugs used to prepare controlled release solid dispersion using EC.

### *2.2. Hydroxypropyl cellulose [HPC]*

HPC is manufactured by treatment of cellulose with sodium hydroxide, followed by a reaction with propylene oxide at an elevated temperature and pressure. It is commercially available in a number of grades having different solution viscosities with molecular weight ranging from 46,000 to 12,46,000. HPC is primarily used in tableting as a binder, film-coating and extended release matrix former. It is also used in microencapsulation process and as a thickening agent. Ozeki et al.[31] prepared controlled release solid dispersion granules of oxeprenolol hydrochloride by solvent evaporation method using EC and four grades of HPC having different molecular weights. The release rate of oxeprenolol hydrochloride decreased with an increasing amount of HPC and becomes almost constant at the composition ratio of 3% and more. The bulk viscosity is related to the molecular weight of HPC and a markedly larger bulk viscosity was observed with a higher molecular weight of HPC. However, there was little noticeable change in release rate and activation energy for the diffusion of oxeprenolol hydrochloride from solid dispersion. In another study, Yuasa et al.[32] investigated the effect of interaction between flurbiprofen and HPC on the release of drug from controlled release solid dispersion. The X-RD pattern and DSC curves showed that flurbiprofen exists in an amorphous state in the solid dispersion. IR spectra confirmed the hydrogen bonding interaction between flurbiprofen and HPC. It has also been observed that the percent of flurbiprofen forming a hydrogen bond with HPC in the solid dispersion increased with decreasing HPC molecular weight or with an increase in the amount of HPC. Moreover a linear relationship was found between the release rate of flurbiprofen and the percent of the hydrogen bonded flurbiprofen in the solid dispersion.

### *2.3. Hydroxypropyl methylcellulose [HPMC]*

HPMC is mixed alkyl hydroalkyl cellulose ether containing methoxy and hydroxypropyl groups. It is prepared by reacting alkali treated cellulose first with methyl chloride to introduce

**Table 1** Drugs used to prepare controlled release solid dispersion using EC.

| Drug | Method of preparation | Release characteristics | Reference |
|---|---|---|---|
| Diclofenac sodium | Freeze drying | Solid dispersions showed slower drug dissolution than the pure drug | [25] |
| Oxeprenolol hydrochloride | Solvent evaporation | The release rate of drug slightly decreased with increasing molecular weight of EC | [26] |
| Indomethacin | Solvent evaporation | Hydrophobic interaction between indomethacin and EC occurred under lower pH region and strongly delayed dissolution of indomethacin | [27] |
| Nifedipine | Phase-separation | Retardation of drug release | [28] |
| Ketoprofen | Spray drying | Prolonged release of drug | [29] |
| Acetaminophen | Solvent evaporation | Drug release decreased as the amount of EC increased in the solid dispersion | [30] |
| Dimenhydrinate | Solvent evaporation | Increase in the amount of EC decreases the drug release rate | [23] |
| Naproxen | Solvent evaporation | Developed formulation showed controlled release of naproxen with a release profile greater than 12 h | [24] |

methoxy groups and then with propylene oxide to introduce propylene glycol ether groups. USP specified four different types of HPMC according to their degree of methoxy and hydroxypropoxy substitution. These are HPMC 1828, HPMC 2208, HPMC 2906 and HPMC 2910. The first two numbers indicate the percentage of hydroxypropoxy groups, determined after drying at 105 °C for 2 h. Swain et al.[33] prepared sustained release solid dispersions of verapamil hydrochloride by solvent evaporation method using polymers like HPMC K4M, Eudragit RSPO and their mixture. FT-IR spectra confirmed the absence of interaction between drug and polymer. In vitro release study showed that the drug release has been extended up to 16 h with solid dispersions containing HPMC; whereas solid dispersion containing Eudragit showed extension up to 10 h and solid dispersion containing both the polymers extended the release up to 12 h respectively. They suggested that HPMC acts as a better release retardant for the model drug. Tanaka et al.[34] investigated in vivo absorption of nilvadipine in dogs by orally administering disintegration controlled matrix tablet [DCMT] containing solid dispersion granules of the drug. The solid dispersion granules were prepared by dissolving HPMC in a mixture of ethanol and dichloromethane, followed by dispersing L-HPC and/or lactose into the solution. Then the solvent was evaporated by a vacuum dryer at 40 °C. In vivo study showed improved solubility and sustained absorption of the drug.

### *2.4. Hydroxypropyl methylcellulose phthalate [HPMCP]*

HPMCP is cellulose in which some of the hydroxyl groups are replaced by methyl ether, 2-hydroxypropyl ether and phthalyl esters. Various types of HPMC are commercially available with molecular weight ranging from 20,000 to 2,00,000. It is widely used in oral tablet or granule formulations as an enteric coating material. It is insoluble in gastric fluid but will swell and dissolve in the upper intestine. Sustained release solid dispersed composite particles were prepared with HPMCP and chitosan, as a carrier using a spray drying method.[35] FT-IR spectroscopy study confirmed the hydrogen bond interaction between the carbonyl group of HPMCP with the amino group of acetaminophen. Spray dried pharmaceutical preparation containing drug, chitosan and HPMCP at their weight ratio of 1:2.5:2.5 delayed the drug release by about 30 times more than that prepared by spray drying method. Similarly, albendazole loaded solid dispersion was prepared using HPMCP as a polymer by solvent evaporation method.[36]

### *2.5. Eudragit*

Polyacrylates and polymethacrylates, the glassy substances, are commonly referred to by the trade name Eudragit. Several types of Eudragit are commercially available and may be obtained as a dry powder, or as an aqueous dispersion, or as an organic solution. The commonly used Eudragits for the preparation of controlled release solid dispersions are Eudragit L, Eudragit RL, Eudragit RS, Eudragit RLPO and Eudragit RSPO. Eudragit L is an anionic copolymerization product of methacrylic acid and methylmethacrylate and is readily soluble in neutral to weakly alkaline water. Eudragit RL and Eudragit RS, are ammonio methacrylate copolymers. Eudragit RL contains 10% of functional quaternary ammonium groups and Eudragit RS possesses 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and are mainly responsible for pH independent permeability of the polymers. The Eudragit RL types are highly permeable compared to the Eudragit RS types. Duarte et al.[37] carried out extensive studies on the influence of polymer combinations such as Eudragit RL and Eudragit RS on the release profile of drug. Formulation containing excess of Eudragit RS caused a slower release of drug than that containing higher amount of Eudragit RL. Moreover, the drug release is controlled by diffusion mechanism and the derived kinetic constant increases with the increase in the content of Eudragit RL in the polymer blend. In another study, sustained release systems of metoprolol

tartrate loaded solid dispersion were prepared using Eudragit RLPO and Eudragit RSPO by melting – solvent method.[38] The drug release from solid dispersion was at a slower rate than from pure drug and from physical mixture. The solid dispersion containing greater amount of Eudragit RSPO showed slower release rates than that containing greater amount of Eudragit RLPO. The release rate of various drugs can be controlled with Eudragit including Nimodipine,[39] Verapamil hydrochloride,[40] Nifedipine,[28] Albendazole.[36]

### 2.6. Polyvinylpyrrolidone-co-vinyl acetate 62 [PVP-VA62]

PVP-VA62 is a copolymer of vinylpyrrolidone and vinylacetate in a ratio of 6:4, manufactured by a free radical polymerization in isopropanol. It is soluble both in extremely hydrophilic liquids such as water and in hydrophobic solvents such as butanol. This polymer is also freely soluble in methylene chloride, chloroform, ethanol, isopropanol and propylene glycol. Verreck et al.[41] prepared solid dispersion of itraconazole and PVP-VA62 by hot stage extrusion method. Release of the drug from the solid dispersion was found to be influenced by processing temperature and pressure.

### 2.7. Other carriers

Many other substances have been tested as carrier for controlled release solid dispersion.

*Terminalia catappa Linn* is a tree belongs to the family *Combretaceae*, largely distributed in tropical and subtropical beaches. The leaves, trunk bark and fruits of the tree have been used as a folk medicine in India. The gum exudates obtained from *T. catappa Linn* are a natural release retarding polymer. The gum exudates obtained from *T. catappa Linn* were reported to sustain the release of dextromethorphan hydrobromide by more than 8 h.[42] The release kinetics showed that the drug release mechanism involved in the matrix is anomalous transport. Ozeki et al.[43] attempted to control the drug release from solid dispersion composed of the polyethylene oxide and carbopol interpolymer complex by varying the carbopol grade. A small release rate was observed with low cross-linked carbopol and middle cross-linked carbopol. Other materials tested for controlled release solid dispersion include pluronic F-66,[44] compritol 888 ATO,[45] poloxamer 188,[9] methyl cellulose,[45] perbutanoyl-β-cyclodextrin,[9] chitosan,[25] kollidon® SR[40] and ethyl vinyl acetate.[39]

## 3. Methods for preparing controlled release solid dispersion

### 3.1. Solvent evaporation method

The solvent evaporation method aims to dissolve the drug and carrier simultaneously in a common solvent, followed by the removal of solvent by evaporation. Identification of a common solvent for both drug and carrier can be problematic and complete solvent removal from the product can be a lengthy process. The solvent can be removed by various processes including vacuum drying, heating of the mixture, slow evaporation of the solvent at low temperature, the rotary evaporators, spray drying and freeze drying. Many polymers and drugs that could not be utilized for the melting method due to their high melting points could be used for solvent evaporation method. Controlled release solid dispersion of oxprenolol hydrochloride was prepared by solvent evaporation method.[48] The drug and polymer were dissolved in ethanol at 46 °C followed by evaporation to make the solid dispersion. The particle sizes of the granules and the drug–polymer ratio have been found to govern the dissolution rate of the drug. Similarly Yuasa et al.[49] prepared sustained release solid dispersion granules of oxprenolol hydrochloride using solvent evaporation method by dissolving or suspending drug in an organic solvent. It has been observed that in a solid dispersion granule composed of 25% oxprenolol hydrochloride, 68% EC and 5% HPC showed the sustained release behavior of drug. Moreover, various dissolution behaviors could be obtained by changing the particle size and the ratio of drug–polymer in the granules. Oxprenolol hydrochloride loaded solid dispersion was also prepared using solvent evaporation method by Ozeki et al.[50] They prepared the solid dispersion by dissolving the drug and polymers at various ratios in ethanol, and the solvent was then evaporated. It was observed that the release rate of oxprenolol hydrochloride reached a minimum level when the content of HPC in the granules was within a range from 5% to 10%. Controlled release solid dispersion of various drugs prepared by the solvent evaporation method is presented in Table 2.

### 3.2. Melting method

The melting method involves melting of a physical mixture of drug and carrier to the liquid state followed by cooling until solidification. However, the method is not suitable for thermolabile drugs and incomplete miscibility is observed between the solid drug and molten carrier. Tran et al.[52] prepared nanoemulsifying Gelucire 28/14 based solid dispersion utilizing melting method for controlled release of aceclofenac. They investigated the dissolution modulating mechanism of alkalinizer [$Na_2CO_3$ and $NaHCO_3$] and polymers [poloxamer 407] for controlled release of drug. Solid dispersion containing alkalizers enhanced the initial release rate of the drug in simulated gastric fluid with precipitation, that was prevented by using poloxamer 407 in the formulation. In another study, Nifedipine tablets were prepared from solid dispersed granules prepared by melting method using PEG4000 as the carrier material.[53] The solubility of nifedipine is too low in aqueous medium. They incorporated the nifedipine as a solid dispersion with PEG 4000 to increase dissolution rate and bioavailability of drug. Carbopol was used as the coating material on both sides of the central matrix containing solid dispersion to provide gel layer which may act as the rate controlling membrane. The DSC thermogram and X-RD pattern indicated the absence of crystalline domain of Nifedipine in solid dispersion. It was observed that the increase in pH, ionic strength and buffer concentration of the dissolution medium decreases the release rate of drug. Rodrigues et al.[54] developed a novel polymeric matrix tablet containing a drug central core for colonic delivery. The central core was formed by a solid dispersion of the drug into the polymer PEG4000 by melting method and compared with that produced using lactose. Less than 30% of the drug was released after 24 h from tablets with lactose central core, whereas almost complete drug release was found from tablet having PEG4000 central core. Moreover, by controlling the temperature of molten PEG4000 solution and the solid dispersion viscosity, the spherical core size can be properly controlled. The solid dispersion tablets were prepared

**Table 2** Preparation of controlled release solid dispersion of drugs by solvent evaporation method.

| Drug | Carrier (s) | Solvent | Solvent removal | Dosage form | Remark | Reference |
|---|---|---|---|---|---|---|
| Nifedipine | HPMC, HPC, Lactose | Dichloromethane, ethanol | Slow evaporation at ambient condition | Tablet | The release of drug was sustained without any recrystallization | [51] |
| Indomethacin | EC, HPMC | Ethanol | Evaporation under reduced pressure using rotary evaporator at 30 °C | – | Hydrophobic interaction between drug and EC occurred at lower pH and strongly delayed the dissolution rate of drug | [27] |
| Flurbiprofen | HPC | Ethanol | Slow evaporation at ambient condition | Granules | The release rate of drug increased with decreasing HPC molecular weight | [32] |
| Oxprenolol hydrochloride | EC, HPC | Ethanol | Slow evaporation at ambient condition | Films | The release rate of drug decreased with increasing HPC concentration and becomes almost constant at the HPC concentration of 3% and more | [31] |
| Dimenhydrinate | EC | Ethanol | Continuous heating on a hot plate | Granules | Crystalline drug was converted into amorphous form in all the solid dispersions | [23] |
| Verapamil hydrochloride | HPMC, Eudragit RSPO | Methanol | Evaporated to dryness in a desiccator under vacuum | – | HPMC acts as a better release retardant for the model drug | [33] |
| Albendazole | HPMC, HPMCP | Ethanol, Dichloromethane | Evaporation at 43 °C in a jacketed beaker connected to a thermostated water bath | – | Elution profile and predicted absorption were extremely pH-dependent | [36] |
| Dextromethorphan hydrobromide | *Terminalia catappa Linn* | Ethanol | Evaporation at reduced pressure at 56 °C with constant stirring | Tablet | Release sustained up to more than 8 h | [42] |
| Nimodipine | Ethyl vinyl acetate, Eudragit RL100, Ethyl acetate | Acetone | Evaporation in a desiccator under vacuum | Tablet | In comparison to pure drug the release has been extended | [39] |
| Nifedipine | Pluronic F-66 | Mixture of acetone, alcohol and water | Spray drying | Pellets | Increase of drug-polymer ratio is proportional to extend of release | [44] |
| Phenacetin | Methyl cellulose, carbopol | Mixture of water and ethanol | Evaporation with an evaporator at 46 °C | – | Release rate depends on the complexation between the polymers | [46] |
| Verapamil hydrochloride | Eudragit RLPO, Kollidon® SR | Acetone | The solvent was removed under vacuum using rotary evaporator within 46 °C | Tablet | Eudragit is found better than the Kollidon® SR in controlling the drug release | [40] |
| Phenacetin | Polyethylene oxide, carbopol | Mixture water and ethanol | Evaporation at 46 °C | – | Polyethylene oxide-carbopol complex controlled the release rate. Degree of crosslinking between the polymers depends on carbopol grade | [43] |

for controlled delivery of sodium ferulate[45] using compritol 888ATO as a carrier by melting method. Matrix tablet prepared by using physical mixture released the drug completely within 12 h, while from the tablets prepared with solid dispersed granules the release was found extended for over 24 h. Similarly, controlled release solid dispersion was prepared by melting method using losartan potassium[9] and metoprolol.[38]

### 3.3. Melting solvent method

The melting solvent method is a combination of the two methods solvent evaporation and melting method. It is performed by dissolving the drug in a suitable solvent and mixing of this solution with the molten carrier followed by cooling for solidification. The advantage of this method is that it requires lower temperatures with lesser risk of decomposition of thermolabile drugs. Chen et al.[55] developed a new concept to combine the solid dispersion technique and osmotic pump technique for water insoluble drug, 10-hydroxycamptothecin to improve solubility with controlled release of drug. The solid dispersion of drug was prepared by the melting solvent method using PEG as the carrier and methanol as the solvent. The optimum formulation was able to deliver drug at a constant rate of 1.21 mg/h for up to 12 h in simulated intestinal fluid, and cumulative release at 12 h was above 90%.

### 3.4. Spray drying

Spray drying is the process where a solution of drug substance and carrier is evaporated by spraying the solution as fine droplets into a chamber under controlled conditions of heat, humidity and air flow. The drying medium is typically air and the product is then separated after completion of drying. Composite particles of acetaminophen with chitosan and HPMCP were prepared by solid dispersion technique using a 4-fluid nozzle spray dryer.[35] Scanning electron micrographs study showed that the spray drying of pharmaceutical preparation can achieve spherical particles with mean particle size of 0.54–13.46 μm. X-ray diffraction and DSC measurement results suggested that acetaminophen and the carriers could not form solid dispersion with simple physical mixing. However spray drying of drug and carriers at certain ratio [acetaminophen: chitosan: HPMCP = 1:2.5:2.5] produced solid dispersion of desired characteristics. The ratio of drug to carrier influenced the degree of crystallinity in the solid dispersions. Similarly, 4 fluid-nozzle spray-drying technique was used for the preparation of controlled release solid dispersion of acetaminophen using chitosan as a carrier.[56] The X-RD study revealed that the drug was amorphous in solid dispersion. Furthermore, the FT-IR spectra confirmed the hydrogen bonding between the carboxyl group of acetaminophen and amino group of chitosan. The resultant formulation containing drug to polymer ratio 1:5 showed sustained release profile in all pH test solutions. Kamada et al.[29] prepared repeat and prolonged release solid dispersion of ketoprofen-HP-β-CD complex and of ketoprofen-EC using spray drying method. They investigated in vitro and in vivo release behavior of this system using rats. It has been observed that the co-administration of the complex and EC solid dispersion gave a constant plasma Ketoprofen level for at least 24 h. In another study, composite solid dispersion particles of salbutamol sulfate were prepared by a 4-fluid nozzle spray drying technique using Eudragit RS or Eudragit RL as a carrier.[57] X-RD patterns revealed that the drug was amorphous and formed a solid dispersion.

### 3.5. Hot melt extrusion

Hot melt extrusion [HME] is a widely used process in plastic, rubber, and food industry. The process has been useful in the preparation of solid dispersion in a single step. Initially HME is used to prepare solid dispersion to enhance solubility of poorly water soluble drugs. Subsequently, its value in developing controlled release preparation has gained more attraction. The advantages of hot-melt extrusion include lower temperature and shorter residence time of the drug carrier mixture. Typically, physical mixture of drug substance and other ingredient is fed into the heated barrel of extruder at a controlled rate. As the physical mixture is conveyed through heated screws, it is transformed into a fluid like state, which allows intimate and homogeneous mixing by the high shear of extruder screws (Figs. 2 and 3). The die then shapes the melt in the required form such as granules, pellets, tablets, sheets, sticks or powder.

Ozawa et al.[58] prepared solid dispersions of water insoluble drug (ethenzamide) and water soluble drug (theophylline) by twin screw extruder method. Solid dispersions obtained by using the twin screw extruder show significantly increased ethenzamide release, but the release rate of theophylline decreased. Theophylline dissolved more rapidly when used alone but when it is used in solid dispersion with carbopol the solubility is reduced and also delayed the drug release due to the interaction between the –N–H of theophylline and –COOH of carbopol. While the rapid dissolution of ethenzamide is observed in the solid dispersion since ethenzamide was completely dispersed which enhances the wettability of drug. The effect of plasticizer level on drug release was investigated from sustained release dosage forms prepared by hot-melt extrusion and film coating using either Eudragit RSPO or Eudragit RD100 as the polymer and triethyl citrate (TEC) as the plasticizer.[59] It was observed that the release rates of both diltiazem hydrochloride and chlorpheneramine maleate increased from hot-melt extrudates with an increase in the TEC level in the formulations. However, the release rate of diltiazem from the Eudragit RS30D-coated pellets decreased with an increase in TEC in the coating dispersion.

### 3.6. Supercritical antisolvent method

In recent years, processing of pharmaceuticals with supercritical fluids has received increased attention. The supercritical fluid exists as a single fluid phase above its critical temperature and critical pressure. Carbon dioxide is the most commonly used supercritical fluid. Depending on the method by which solution and supercritical fluid are introduced and mixed into each other, different terminology have been used by different researchers: (a) precipitations from supercritical solutions by rapid expansion of supercritical solution,[60] (b) precipitation from saturated solution using supercritical fluid as an antisolvent,[61] (c) precipitation from gas saturated solutions.[62,63] Supercritical antisolvent related to various processes may be aerosol solvent extraction system (ASES),[64,65] solution enhanced dispersion by supercritical fluids (SEDS),[66,67] gas antisolvent (GAS),[68] and supercritical antisolvent (SAS).[69]

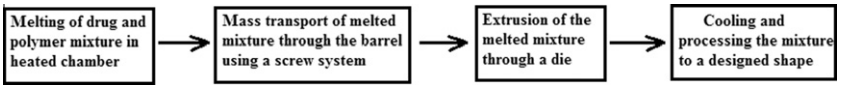


**Figure 2** Stages of hot melt extrusion process.

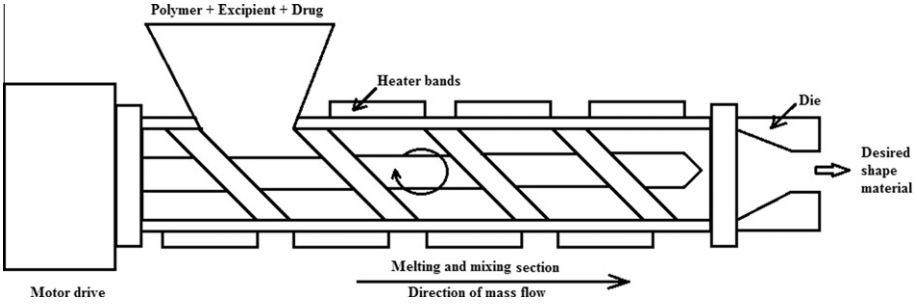


**Figure 3** Schematic diagram of hot melt extrusion.

Schematic diagram of the supercritical antisolvent apparatus is shown in Fig. 4.

In GAS or SAS process a mixture of drug and polymer is sprayed through an atomizer into a chamber filled with supercritical fluids. The expansion and extraction of organic solvent into the compressed gas result in lowering the solvent power of organic solvent for drug and polymer leading to precipitation. Duarte et al.[37] prepared acetazolamide composite microparticles by supercritical anti-solvent technique using Eudragit RS100 and RL100 as carriers for ophthalmic drug delivery. The composite particles in the size range of 8–40 μm were produced by semi-continuous process and batch process. Particles prepared by the batch process had a mean diameter larger than that produced by semi-continuous process. Composite particles containing Eudragit RS led to a slower release of drug than those containing Eudragit RL. Moreover, particles prepared by batch process exhibited faster release than those prepared by the semi-continuous process.

### *3.7. Other methods*

Huang et al.[70] prepared matrix type microparticles containing solid dispersion of nifedipine with polymers by phase separation method for controlled drug delivery. It was observed that the microparticles' size, morphology, and size distribution were not affected by drug loading. At lower levels of drug loading, nifedipine release was well described by the Beker and Lonsdale's matrix diffusion model. However, at higher levels of drug loading a change in the release kinetics was observed. Dangprasirt and Pongwai[25] prepared diclofenac sodium loaded controlled release solid dispersion powders and capsules by freeze-drying technique using EC and chitosan as carriers. In vitro release study indicated that the ratio of EC and chitosan was an important factor in controlling the dissolution of the solid dispersion. Ikeda et al.[47] prepared controlled release solid dispersion of captopril by kneading method using a combination of hydrophilic and hydrophobic cyclodextrin derivatives. It has been observed that a combination of hydrophilic and hydrophobic cyclodextrin was useful for controlling the drug release.

## 4. Mathematical modeling of drug release from controlled release solid dispersion based systems

In order to establish the mathematical modeling of drug release, the experimental data are fitted to different kinetic models. Various mathematical kinetic models like zero order, first order, Higuchi, Hixson-crowell, etc. tried to justify the mechanism of drug release. The commonly used mathematical models for evaluating the release kinetics of drug are shown in Table 3.

Higuchi developed several theoretical models to describe the release rate of water soluble and poorly soluble drugs from matrix system. Initially, it was valid only for planar systems. However, later it has been modified and extended to different geometrics and matrix systems including porous structures. Various researchers have used the Higuchi model to interpret their experimental drug release from solid dispersion system. Ozeki et al.[50] investigated the effect of the composition ratios between polymer and drug (oxprenolol hydrochloride) on the release mechanism by using Higuchi and Baker–Lonsdale model. The formulation, containing not more than 20% of drug, released for a longer period of time and obeyed the Higuchi and Baker–Lonsdale model. However, at 30% or more of drug, the release rate did not obey the above mentioned model.

Korsmeyer developed semi-empirical equation to describe drug release from polymeric system

$$\frac{M_t}{M_\alpha} = kt^n$$

where $k$ is a constant incorporating structural and geometric characteristic of the system, $M_t/M_\alpha$ is the fraction release of drug at time $t$, and $n$ is the release exponent, indicative of the drug release mechanism. Peppas characterized different release mechanisms by using this $n$ value. The above equation can be applied in two situations: [a] where $n = 0.5$ indicating diffusion-controlled drug release [b] $n = 1.0$ indicating swelling controlled drug release. Moreover, the values of n between 0.5 and 1 can be regarded as an indicator for the superposition of both phenomena [anomalous transport]. The diffusional exponent is dependent on the geometry of the device as well as the release mechanism of drug [Table 4].[71–73]

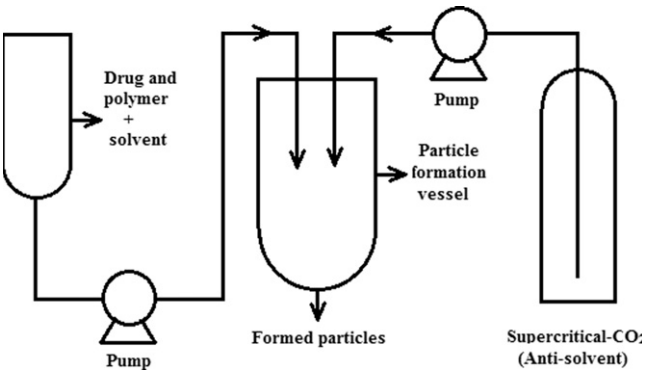


**Figure 4** Schematic diagram of the supercritical antisolvent apparatus.

Ozeki et al.[46] used the Korsmeyer–Peppas model to describe drug release from controlled release methylcellulose-carboxyvinylpolymer interpolymer complex solid dispersion.

It was observed that the solid dispersion containing the lowest molecular weight of methylcellulose showed n value of approximately 1. As the molecular weight of methylcellulose increased the n value decreased with improved drug release. In another study, Korsmeyer–Peppas model was applied to gain information about the release mechanism of drug from the solid dispersion systems having various molecular weights of ethyl cellulose. In case of drug and ethyl cellulose binary system molecular weight of ethyl cellulose did not influence the n value, it was found to be about 0.4. However, in a ternary system containing drug, ethyl cellulose and hydroxypropyl cellulose the n value increased with increasing molecular weight of ethyl cellulose and reached 0.5. The results indicated that

**Table 3** Commonly used mathematical model for evaluating the release kinetics of drug.

| S.N. | Mathematical model name | Mathematical equation | Terms used in equation |
|---|---|---|---|
| 1 | Zero order | $Q_t = Q_0 - K_0 t$ | $Q_t$ = amount of drug remaining as a solid state at time $t$; $Q_0$ = initial amount of drug in the pharmaceutical dosage form; $K_0$ = zero-order release rate constant |
| 2 | First-order | $\log Q_t = \log Q_0 - \frac{K_1 t}{2.303}$ | $Q_t$ = amount of drug remaining as a solid state at time $t$; $Q_0$ = initial amount of drug in the pharmaceutical dosage form; $K_1$ = First-order release rate constant |
| 3 | Higuchi | $Q_t = K_H t$ | $Q_t$ = amount of drug released in time $t$; $K_H$ = Higuchi's release rate constant |
| 4 | Hixson-crowell | $Q_0^{1/3} - Q_t^{1/3} = K_S t$ | $Q_t$ = amount of drug remaining as a solid state at time $t$; $Q_0$ = initial amount of drug in the pharmaceutical dosage form; $K_s$ = Release rate constant |
| 5 | Baker–Lonsdale | $\frac{3}{2}[1-(1-\frac{M_t}{M_\alpha})^{2/3}] - \frac{M_t}{M_\alpha} = \frac{3D_m C_{ms}}{r_0^2 C_0} t$ | $M_t$ = amount of drug released at time $t$; $M_\alpha$ = amount of drug released at an initial time; $D_m$ = diffusion coefficient; $C_{ms}$ = drug solubility in the matrix; $r_0$ = radius of the spherical matrix; $C_0$ = initial concentration of drug in the matrix |
| 6 | Korsmeyer–peppas | $\frac{M_t}{M_\alpha} = at^n$ | $M_t/M_\alpha$ = fraction of drug released at time $t$; $a$ = kinetic constant; $n$ = diffusional release exponent |
| 7 | Hopfenberg | $\frac{M_t}{M_\alpha} = 1 - [1 - \frac{K_0}{C_0 a_0}]^n$ | $M_t/M_\alpha$ = fraction of drug dissolved; $K_0$ = erosion rate constant; $C_0$ = initial concentration of drug in the matrix; $a_0$ = initial radius for matrix; $n$ = 1, 2 and 3 for a slab, cylinder and sphere, respectively. |
| 8 | Poiseuille's law of laminar flow | $\frac{dM}{dt} = \frac{\pi c}{8}\frac{r^4}{\eta}\frac{P_1 - P_2}{h}$ | dM/dt = drug release rate; $c$ = concentration of drug in matrix; $r$ = radius of orifice; $\eta$ = viscosity of matrix; $P_1$–$P_2$ = pressure difference between the inside and outside of the membrane. |
| 9 | Weibull | $\log[-\ln(1-m)] = b\log(t - T_i) - \log a$ | $m$ = fraction of the drug in solution at time $t$; $a$ = time scale of the process; $b$ = shape parameter; $T_i$ = lag time |

**Table 4** Drug release mechanisms and diffusion exponent for polymeric controlled delivery systems of different geometries.

| Release exponent [$n$] Thin film | Cylinder | Sphere | Drug transport mechanism |
|---|---|---|---|
| 0.5 | 0.44 | 0.42 | Fickian diffusion |
| $0.5 < n < 1.0$ | $0.44 < n < 0.89$ | $0.42 < n < 0.85$ | Anomalous transport |
| 1.0 | 0.89 | 0.85 | Case-II transport |

**Table 5** Release kinetics of various drugs from controlled release solid dispersion system.

| Drug | Polymer(s) | Dosage form | Kinetics model | Observation | References |
|---|---|---|---|---|---|
| Nilvadipine | HPMC, HPC | Tablet | Hixon-crowell | The release of drug is disintegration limited | 51 |
| Dimenhydrinate | Ethylcellulose | Granules | First order | Good fit to first order kinetics. The linearity of the drug release is proportional to the content of ethylcellulose following zero-order kinetic | 23 |
| Captopril | Cyclodextrins | Solid complex | Korsmeyer–Peppas | Initial drug release follows dissolution mechanisms, subsequent drug release is controlled by a diffusion mechanism. | 47 |
| Sodium diclofenac | PEG 400, Eudragit RS 100 | Tablet | Korsmeyer–Peppas | The release exponent values of all the formulations are greater than one. | 54 |
| Nifedipine | PEG 400 | Tablet | Korsmeyer–Peppas | Different formulations showing different n values from 0.33–0.55. | 53 |
| Indomethacin | EC, HPMC | Solid dispersion | Higuchi | Release of indomethacin followed diffusional mechanisms whose dissolution rate constants are pH depended. | 27 |
| Oxprenolol hydrochloride | EC, HPC | Solid dispersion films | Fick's second law | The resistance to diffusion of drug from the swollen HPC gel of the solid dispersion was almost the same regardless of the molecular weight of HPC. | 31 |
| 10-hydroxy camptothecin | PEG 400 | Tablet | Poiseuille's law of laminar flow | The tablet prepared from solid dispersion has great potential in the controlled delivery of water insoluble drugs | 55 |
| Metoprolol | Eudragit RLPO, Eudragit RSPO | Solid dispersed particle | Zero-order, Higuchi | The formulation containing greater ratios of Eudragit RSPO showed slower release rates than that containing greater ratios of Eudragit RLPO | 38 |
| Nifedipine | Pluronic F-66 | Pellets | First-order | Pellets of solid dispersion showed a 12 h release profile following first-order kinetics. | 74 |
| Diclofenac sodium | Ethylcellulose | Capsule | First-order | The dissolution of the solid dispersion powder and capsules was closer to a first-order model than to a zero-order or diffusion control model | 25 |
| Indomethacin | Eudragit | Granules | Higuchi, First-order | The release process is diffusion controlled and dependent on the initial drug concentration | 75 |
| Phenylpropanolamine HCl | ATO 888 | Tablet | Higuchi | The drug release followed the diffusion controlled model | 76 |

the release of drug from these solid dispersions followed the diffusion theory. Kumar et al.[42] investigated the effect of formulation variables on the resulting n value of a sparingly soluble model drug, dextromethorphan hydrobromide. It has been observed that release kinetics of the drug from the system was found to be anomalous transport with n values between 0.44 and 0.89.

Baker and Lonsdale's release model was used for data analysis of controlled release molecular dispersion of Eudragit and ethylcellulose binary blends.[28] According to this model the effect of the ratio of the Eudragit to ethylcellulose on the drug release rate was analyzed by using two major parameters-particle size [$1/r^2$] and diffusion coefficient [$D$]. The matrix permeability expressed in terms of the effective drug diffusion coefficient was increased by increasing the ratio of Eudragit to ethylcellulose. Moreover, an increase in the ratio of Eudragit to ethyl cellulose resulted an upward trend in release rate. Further analysis was performed to examine the effect of $D$ and $1/r^2$, and of only $D$ on drug release. The former was found more influencing. The most commonly used mathematical models describing the release kinetics of various drugs from controlled release solid dispersion systems are shown in Table 5.

## 5. Conclusion

Solid dispersion systems have been utilized during the past four decades to increase dissolution rate and bioavailability of poorly soluble drugs. In recent years in addition to dissolution rate and bioavailability enhancement great attention has been paid to use solid dispersion for the development of controlled release dosage forms. The solid dispersions have tremendous potential in the area of controlled release dosage form design because of the wide availability of a variety of carriers those are either poorly soluble or swellable in aqueous medium. These carriers include ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carbopol, Eudragit, etc. The judicious application of insoluble polymer and/or water swellable polymer can retard the release pattern of a drug to a desired extent. It is considered that the water soluble polymer swells in water and is trapped by the water insoluble polymer resulting in retardation of drug release. Various methods successfully used for the preparation of controlled release solid dispersion in the lab scale have been reviewed in this article. However, scale-up of solid dispersion technology from lab scale to industrial scale is limited. The application of hot melt extrusion and supercritical fluid technology for the production of controlled release solid dispersion is particularly an important breakthrough for scale-up of solid dispersion manufacture. The great advantage of controlled release solid dispersion is its monolithic structure that avoids the risk of burst release. The release of drug from controlled release solid dispersion is dependent upon the molecular weight and concentration of carriers, drug-polymer ratio and crosslinking degree of polymer. Proper selection of carrier and accurate mathematical modeling are also keys to control the release profile of drug. However, many parameters in the current mathematical models are unknown and need to be identified in order to accurately predict drug release profiles. Despite several efforts many troubles and challenges still remain unexplored in developing controlled release solid dispersion systems. Even so, as the research advances, the solid dispersion will be one of the exciting frontiers of controlled release drug delivery systems.

## References


1. Linn M, Collonot EM, Djuric D, Hempel K, Fabian E, Kolter K, et al. Soluplus® as an effective absorption enhancer of poorly soluble drugs in vitro and in vivo. *Eur J Pharm Sci* 2012;**45**(3):336–43.
2. Kim MS, Kim JS, Park HJ, Cho WK, Cha KH, Hwang SJ. Enhanced bioavailability of sirolimus via preparation of solid dispersion nanoparticles using a supercritical antisolvent process. *Int J Nanomedicine* 2011;**6**:2997–3009.
3. Chen Y, Shi Q, Chen Z, Zheng J, Xu H, Li J, et al. Preparation and characterization of emulsified solid dispersions containing docetaxel. *Arch Pharm Res* 2011;**34**(11):1909–17.
4. Yan YD, Sung JH, Kim KK, Kim DW, Kim JO, Lee BJ, et al. Novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes. *Int J Pharm* 2012;**422**(1–2): 202–10.
5. Tung NT, Park CW, Oh TO, Kim JY, Ha JM, Park ES. Formulation of solid dispersion of rebamipide evaluated in a rat model for improved bioavailability and efficacy. *J Pharm Pharmacol* 2011;**63**(12):1539–47.
6. Wu JX, Yang M, Berg F, Pajander J, Rades T, Rantanen J. Influence of solvent evaporation rate and formulation factors on solid dispersion physical stability. *Eur J Pharm Sci* 2011;**44**(5): 610–20.
7. Moes JJ, Koolen SL, Huitema AD, Schellens JH, Beijnen JH, Nuijen B. Pharmaceutical development and preliminary clinical testing of an oral solid dispersion formulation of docetaxel (ModraDoc001). *Int J Pharm* 2011;**420**(2):244–50.
8. Kovacic B, Vrecer F, Planinsek O. Design of a drug delivery system with bimodal pH dependent release of a poorly soluble drug. *Pharmazie* 2011;**66**(6):465–6.
9. Tran HTT, Park JB, Hong KH, Choi HG, Han HK, Lee J, et al. Preparation and characterization of pH-independent sustained release tablet containing solid dispersion granules of a poorly water soluble drug. *Int J Pharm* 2011;**415**(1–2):83–8.
10. Kanaujia P, Lau G, Ng WK, Widjaja E, Hanefeld A, Fischbach M, et al. Nanoparticle formation and growth during in vitro dissolution of ketoconazole solid dispersion. *J Pharm Sci* 2011;**100**(7):2876–85.
11. Patel MR, San Martin-Gonalez MF. Characterization of ergocalciferol loaded solid lipid nanoparticles. *J Food Sci* 2012;**77**(1): N8–N13.
12. Perge L, Robitzer M, Guillemot C, Devoisselle JM, Quignard F, Legrand P. New solid lipid microparticles for controlled ibuprofen release: formulation and characterization study. *Int J Pharm* 2012;**422**(1–2):59–67.
13. Kim HJ, Lee SH, Lim EA, Kim JS. Formulation optimization of solid dispersion of mosapride hydrochloride. *Arch Pharm Res* 2011;**34**(9):1467–75.
14. Attama AA, Igbonekwu CN. In vitro properties of surface-modified solid lipid microspheres containing an antimalarial drug: halofantrine. *Asian Pac J Trop Med* 2011;**4**(4):253–8.
15. Bikiaris DN. Solid dispersions. Part I: recent evolutions and future opportunities in manufacturing methods for dissolution rate enhancement of poorly water-soluble drugs. *Expert Opin Drug Deliv* 2011;**8**(11):1501–19.
16. Iqbal B, Ali A, Ali J, Baboota S, Dang S, Shadab M, et al. Recent advances and patents in solid dispersion technology. *Recent Pat Drug Deliv Formul* 2011;**5**(3):244–64.
17. Srinarong P, De WH, Frijlink HW, Hinrichs WL. Improved dissolution behavior of lipophilic drugs by solid dispersions: the

production process as starting point for formulation considerations. *Expert Opin Drug Deliv* 2011;**8**(9):1121–40.
18. Warren DB, Benameur H, Porter CJ, Pouton CW. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: a mechanistic basis for utility. *J Drug Target* 2010;**18**(10):704–31.
19. Tran PH, Tran TT, Lee KH, Kim DJ, Lee BJ. Dissolution-modulating mechanism of pH modifiers in solid dispersion containing weakly acidic or basic drugs with poor water solubility. *Expert Opin Drug Deliv* 2010;**7**(5):647–61.
20. Qian F, Huang J, Hussain MA. Drug-polymer solubility and miscibility: stability consideration and practical challenges in amorphous solid dispersion development. *J Pharm Sci* 2010;**99**(7):2941–7.
21. Janssens S, Van den Mooter G. Review: physical chemistry of solid dispersions. *J Pharm Pharmacol* 2009;**61**(12):1571–86.
22. Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersion: a review. *Pak J Pharm Sci* 2009;**22**(2):234–46.
23. Desai J, Alexander K, Riga A. Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. *Int J Pharm* 2006;**308**:115–23.
24. Iqbal Z, Babar A, Ashraf M. Controlled-release naproxen using micronized ethyl cellulose by wet-granulation and solid-dispersion method. *Drug Dev Ind Pharm* 2002;**28**(2):129–34.
25. Dangprasirt P, Pongwai S. Development of diclofenac sodium release solid dispersion powders and capsules by freeze drying technique using ethylcellulose and chitosan as carriers. *Drug Dev Ind Pharm* 1998;**24**(10):947–53.
26. Ozeki T, Yuasa H, Kanaya Y, Oishi K. Application of the solid dispersion method to the controlled release of medicine. VII. Release mechanism of a highly water-soluble medicine from solid dispersion with different molecular weights of polymer. *Chem Pharm Bull* 1995;**43**(4):660–5.
27. Ohara T, Kitamura S, Kitagawa T, Terada K. Dissolution mechanism of poorly water-soluble drug from extended release solid dispersion system with ethylcellulose and hydroxypropylmethylcellulose. *Int J Pharm* 2005;**302**:95–102.
28. Huang J, Wigent RJ, Schwartz JB. Nifedipine molecular dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blends for controlled drug delivery: effect of matrix composition. *Drug Dev Ind Pharm* 2006;**32**:1185–97.
29. Kamada M, Hirayama F, Udo K, Yano H, Arima H, Uekama K. Cyclodextrin conjugate-based controlled release system: repeated and prolonged-release of ketoprofen after oral administration in rats. *J Control Release* 2002;**82**:407–16.
30. Ghaly ES, Hernandez JI, Malave A, Marti A. Ethylcellulose as a carrier for controlled-release acetaminophen tablets. *P R Health Sci J* 1992;**11**(3):159–62.
31. Ozeki T, Yuasa H, Kanaya Y, Oishi K. Application of the solid dispersion method to the controlled release of medicine. VIII. Medicine release and viscosity of the hydrogel of a water-soluble polymer in a three-component solid dispersion system. *Chem Pharm Bull* 1995;**43**(9):1574–9.
32. Yuasa H, Ozeki T, Takahashi H, Kanaya Y, Ueno M. Application of the solid dispersion method to the controlled release of medicine. VI. Release mechanism of a slightly water soluble medicine and interaction between flurbiprofen and hydroxypropyl cellulose in solid dispersion. *Chem Pharm Bull* 1994;**42**(2):354–8.
33. Swain SK, Patra CN, Sruti J, Rao MEB. Design and evaluation of sustained release solid dispersions of verapamil hydrochloride. *Int J Pharm Sci Nanotechnol* 2011;**3**(4):1252–62.
34. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ibuki R, et al. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): in vivo evaluation. *J Control Release* 2006;**112**:51–6.
35. Chen R, Takahashi H, Okamoto H, Danjo K. Particle design of three-component system for sustained release using a 4-fluid nozzle spray-drying technique. *Chem Pharm Bull* 2006;**54**(11):1486–90.
36. Sugawara M, Kadomura S, He X, Takekuma Y, Kohri N, Miyazaki K. The use of an in vitro dissolution and absorption system to evaluate oral absorption of two weak bases in pH-independent controlled-release formulation. *Eur J Pharm Sci* 2005;**26**:1–8.
37. Duarte ANC, Roy C, Gonzalez AV, Duarte CMM, Paternault PS. Preparation of acetazolamide composite microparticles by supercritical anti-solvent techniques. *Int J Pharm* 2007;**332**:132–9.
38. Varshosaz J, Faghihian H, Rastgoo K. Preparation and characterization of metoprolol controlled-release solid dispersions. *Drug Deliv* 2006;**13**:295–302.
39. Rathinaraj BS, Rajeevr C, Choudhury PK, Gannesh SB, Shinde GV. Studies on dissolution behaviour of sustained release solid dispersions of nimodipine. *Int J Pharm Sci Rev Res* 2010;**3**(1):77–82.
40. Sahoo J, Murthy PN, Biswal S, Manik. Formulation of sustained-release dosage form of verapamil hydrochloride by solid dispersion technique using Eudragit RLPO or Kollidon® SR. AAPS Pharm Sci Tech 2009;10(1):27–33.
41. Verreck G, Decorte A, Heymans K, Adriaensen J, Cleeren D, Jacobs A, et al. The effect of pressurized carbon dioxide as a temporary plasticizer and foaming agent on the hot stage extrusion process and extrudate properties of solid dispersions of itraconazole with PVP-VA 64. *Eur J Pharm Sci* 2005;**26**: 349–58.
42. Kumar SV, Sasmal D, Pal SC. Rheological characterization and drug release studies of gum exudates of *Terminalia catappa Linn*. *AAPS Pharm Sci Tech* 2008;**9**(3):885–90.
43. Ozeki T, Yuasa H, Kanaya Y. Controlled release from solid dispersion composed of poly(ethylene oxide)-Carbopol® interpolymer complex with various cross-linking degrees of Carbopol®. *J Control Release* 2000;**63**:287–95.
44. Ho HO, Chen CN, Sheu MT. Influence of pluronic F-68 on dissolution and bioavailability characteristics of multiple-layer pellets of nifedipine for controlled release delivery. *J Control Release* 2000;**68**:433–40.
45. Li FQ, Hu JH, Deng JX, Su H, Xu S, Liu JY. In vitro controlled release of sodium ferulate from compritol 888 ATO-based matrix tablets. *Int J Pharm* 2006;**324**:152–7.
46. Ozeki T, Yuasa H, Okada H. Controlled release of drug via methylcellulose-carboxyvinylpolymer interpolymer complex solid dispersion. *AAPS Pharm Sci Tech* 2005;**6**(2):E231–6.
47. Ikeda Y, Kimura K, Hirayama F, Arima H, Uekama K. Controlled release of a water-soluble drug, captopril, by a combination of hydrophilic and hydrophobic cyclodextrin derivatives. *J Control Release* 2000;**66**:271–80.
48. Yuasa H, Ozeki T, Kanaya Y, Oishi K. Application of the solid dispersion method to controlled release of medicine. II. Sustained release tablet using solid dispersion granule and the medicine release mechanism. *Chem Pharm Bull* 1992;**40**(6):1592–6.
49. Yuasa H, Ozeki T, Kanaya Y, Oishi K, Oyake T. Application of the solid dispersion method to controlled release of medicine. I. Controlled release of water soluble medicine by using solid dispersion. *Chem Pharm Bull* 1991;**39**(2):465–7.
50. Ozeki T, Yuasa H, Kanaya Y, Oishi K. Application of the solid dispersion method to controlled release of medicine. V. Suppression mechanism of the medicine release rate in the three-component solid dispersion system. *Chem Pharm Bull* 1994;**42**(2): 337–43.
51. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ohike A, et al. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine. *J Control Release* 2005;**108**:386–95.
52. Tran TTD, Tran PHL, Lee BJ. Dissolution-modulating mechanism of alkalizers and polymers in a nanoemulsifying solid

dispersion containing ionizable and poorly water-soluble drug. *Eur J Pharm Biopharm* 2009;**72**:83–90.
53. Hong SI, Oh SY. Dissolution kinetics and physical characterization of three-layered tablet with poly(ethylene oxide) core matrix capped by carbopol. *Int J Pharm* 2008;**356**:121–9.
54. Rodriguez MLG, Maestrelli F, Mura P, Rabasco AM. In vitro release of sodium diclofenac from a central core matrix tablet aimed for colonic drug delivery. *Eur J Pharm Sci* 2003;**20**:125–31.
55. Chen H, Jiang G, Ding F. Monolithic osmotic tablet containing solid dispersion of 10-hydroxycamptothecin. *Drug Dev Ind Pharm* 2009;**35**:131–7.
56. Chen R, Okamoto H, Danjo K. Particle design using a 4-fluid-nozzle spray-drying technique for sustained release of acetaminophen. *Chem Pharm Bull* 2006;**54**(7):948–53.
57. Chen R, Okamoto H, Danjo K. Preparation of functional composite particles of salbutamol sulfate using a 4-fluid nozzle spray-drying technique. *Chem Pharm Bull* 2008;**56**(3):254–9.
58. Ozawa M, Hasegawa K, Yonezawa Y, Sunada H. Preparation of solid dispersion for ethenzamide-carbopol and theophylline-carbopol systems using a twin screw extruder. *Chem Pharm Bull* 2002;**50**(6):802–7.
59. Zhu Y, Mehta KA, McGinity JW. Influence of plasticizer level on the drug release from sustained release film coated and hot-melt extruded dosage forms. *Pharm Dev Technol* 2006;**11**(3):285–94.
60. Kakumanu VK, Bansal AK. Supercritical fluid technology in pharmaceutical research. *CRIPS* 2003;**4**:8–12.
61. Hanna M, York P. Method and apparatus for the formation of particles. WO9501221 (1995).
62. Sencar-Bozic P, Srcic S, Knez Z, Kerc J. Improvement of nifedipine dissolution characteristics using supercritical $CO_2$. *Int J Pharm* 1997;**148**:123–30.
63. Kerc J, Srcic S, Sencar-Bozic P. Micronization of drugs using supercritical carbon dioxide. *Int J Pharm* 1999;**182**:33–9.
64. Jung J, Perrut M. Particle design using supercritical fluids: literature and patent survey. *J Supercrit Fluid* 2001;**20**:179–219.
65. Bleich J, Muller BW. Production of drug loaded microparticles by the use of supercritical gases with the aerosol solvent extraction system (ASES) process. *J Microencapsul* 1996;**13**:131–9.
66. Juppo AM, Boiddier C, Khoo C. Evaluation of solid dispersion particles prepared with SEDS. *Int J Pharm* 2003;**250**:385–401.
67. Palakodaty S, York P, Pritchard J. Supercritical fluid processing of materials from aqueous solutions: the application of SEDS to lactose as a model substance. *Pharm Res* 1998;**15**:1835–43.
68. Randolph TW, Randolph AD, Mebes M, Yeung S. Sub-micrometer-sized biodegradable particles of poly(L-lactic acid) via the gas antisolvent spray precipitation process. *Biotechnol Prog* 1993;**9**:429–35.
69. Elvassore N, Baggio M, Pallado P, Bertucco A. Production of different morphologies of biocompatible polymeric materials by supercritical $CO_2$ antisolvent techniques. *Biotechnol Bioeng* 2001;**73**:449–57.
70. Huang J, Wigent RJ, Bentzley CM, Schwartz JB. Nifedipine solid dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend for controlled drug delivery effect of drug loading on release kinetics. *Int J Pharm* 2006;**319**:44–54.
71. Ritger PL, Peppas NA. A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J Control Release* 1987;**5**:23–36.
72. Ritger PL, Peppas NA. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. *J Control Release* 1987;**5**:37–42.
73. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Reviews* 2001;**48**:139–57.
74. Mehta KA, Kislalioglu MS, Phuapradit W, Malick AW, Shah NH. Multi-unit controlled release systems of nifedipine and nifedipine: pluronic F-68 solid dispersions: characterization of release mechanisms. *Drug Dev Ind Pharm* 2002;**28**(3):275–85.
75. Khanfar MS, Salem MS, Najib NM, Pillai GK. Dissolution behavior of sustained release formulations of indomethacin with Eudragit RS. *Acta Pharm Hung* 1997;**67**(6):235–9.
76. Perez MA, Ghaly ES, Marti A. Sustained release phenylpropanolamine hydrochloride from ATO 888 matrix. *P R Health Sci J* 1993;**12**(4):263–7.